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Re: 6486-89536

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This is to certify that a professional translator on our staff who is skilled in the Japanese language translated the enclosed Japanese Kokoku Patent No. Sho 45[1970]-14291 from Japanese into English.

We certify that the attached English translation conforms essentially to the original Japanese language.

K Vitray

Kim Vitray
Operation Manager

Subscribed and sworn to before me this 9 day of SEPTEMBER, 2002.

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My Commission Expires
December 08, 2003

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Japanese Kokoku Patent No. Sho 45[1970]-14291

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NOVEL CINNAMIC ACID AMIDE MANUFACTURING METHOD

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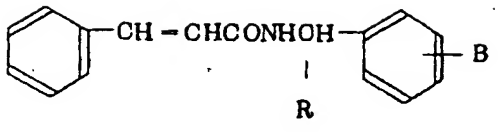
Detailed explanation of the invention

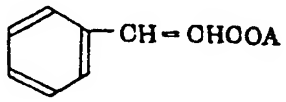
The present invention relates to a method for the manufacture of a novel cinnamic acid amide represented by the general formula (I):



(I)

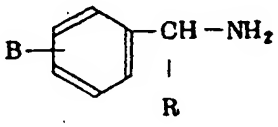
(in this formula, R represents a lower alkyl group, and B represents an oxy group, a lower alkoxyl group, a lower alkyl group, a nitro group or a halogen atom).

To explain more specifically, the present invention relates to a method to obtain a novel cinnamic acid amide represented by the general formula (I) given previously by the reaction of cinnamic acid or its reactive derivatives represented by the general formula (II):



(II)

(in this formula, A represents an oxy group, a halogen atom, or a lower alkoxyl group) and a substituted α-lower alkylbenzylamine represented by the general formula (III):



(III)

(in this formula, R and B are the same as described above).

The compounds obtained by the method of the present invention are novel compounds not described in the literature. The present substance group has remarkable [blood] pressure reduction, anti-inflammation, and pain-relieving effects.

The objective of the present invention is the manufacture of useful compounds in an industrially advantageous manner.

As feedstock substances that can be used in the method of the present invention, for example, those having the following substituent groups are available. That is:

B: hydroxy, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, fluorine, chlorine, bromine, iodine, nitro,

R: methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl,

A: hydroxy, chlorine, bromine, iodine, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, and so on can be mentioned.

Next, embodiments of the reaction will be explained individually. When using cinnamic acid, approximately equivalent molar amounts of cinnamic acid and amine are reacted with a dehydrating aid, such as dimethyl, ethyl, propyl, butyl or other alkyl carbodiimides; diphenyl

carbodiimide, dibenzyl carbodiimide, dicyclopentyl, hexyl, heptyl or other alkyl carbodiimides; or the like in an appropriate solvent, such as benzene, toluene, xylene, or other aromatic hydrocarbons; petroleum ether, petroleum benzene, ligroin, gasoline, pentane, hexane, heptane, cyclopentane, cyclohexane, cycloheptane, or other aliphatic hydrocarbons; ethyl ether, propyl ether, tetrahydrofuran, dioxane, or other ethers; methyl acetate, ethyl acetate, propyl acetate, butyl acetate or other esters; acetone, methyl ethyl ketone, methyl butyl ketone or other ketones; dichloromethane, dichloroethane, chloroform, carbon tetrachloride, or other haloalkanes; methyl alcohol, ethyl alcohol or other alcohols, to obtain the desired products. Furthermore, it is also acceptable that cinnamic acid and amine may be heated and reacted with an ion-exchange resin, such as IRA-400 or other anion-, cation-exchange resin, and benzene, toluene, xylene or the like, and if necessary, using a water separator. Furthermore, cinnamic acid and amine may be heated and reacted with, for example, p-toluenesulfonic acid, p-toluenesulfonic acid chloride or the like and benzene, toluene, xylene, chloroform, carbon tetrachloride, pyridine, lutidine or the like, and if necessary, using a water separator, to obtain the desired products. Moreover, a mixture of cinnamic acid and amine may be simply heated or distilled in the presence or absence of a dehydrating agent to obtain the desired product.

When using a lower alkyl ester of cinnamic acid, this can react with amine in the absence of a solvent or, if necessary, in a solvent like benzene, toluene, xylene, or other aromatic hydrocarbons; petroleum ether, petroleum benzene, gasoline, ligroin, pentane, hexane, heptane, cyclopentane, cyclohexane, cycloheptane, or other aliphatic hydrocarbons; methyl alcohol, ethyl alcohol, propyl alcohol, butyl alcohol or other alcohols; ether, tetrahydrofuran, dioxane, or the like in the absence of a catalyst or, if necessary, in the presence of methylate, ethylate, propylate, butylate and so on of lithium, sodium, potassium and so on or other alkali catalysts; pyridine, lutidine, picoline, trimethylamine, triethylamine, dimethyl aniline, diethyl aniline, or other tertiary organic amines as a catalyst in a heating range of 50°C to 400°C under atmospheric pressure or in an autoclave for 30 min to about one month or so to achieve the objective. It is desirable that the alcohol formed during the reaction is removed out of the system. However, it is not necessary to do so.

The reaction with cinnamic acid halide can be carried out by using thionyl chloride, phosgene, acid chloride, acid bromide or the like manufactured by other methods in an appropriate solvent, such as benzene, toluene, xylene, or other aromatic hydrocarbons; petroleum ether, petroleum benzene, ligroin, gasoline, pentane, hexane, heptane, cyclopentane, cyclohexane, cycloheptane, or other aliphatic hydrocarbons; chloroform, carbon tetrachloride, or other haloalkanes; acetone, methyl ethyl ketone, methyl butyl ketone or other ketones; methyl acetate, ethyl acetate, propyl acetate, butyl acetate or other esters; with lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium

carbonate, calcium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, or other alkali metal or alkaline-earth metal compounds, or pyridine, picoline, lutidine, trimethylamine, triethylamine, dimethyl aniline, diethyl aniline, or other tertiary amine as a promoter, to obtain the desired products in an extremely easy manner.

An explanation will be given on the basis of application examples in the following. However, these examples are not restrictive.

Application Example 1

14.8 g of cinnamic acid, 13.5 g of α-p-dimethylbenzylamine, and 0.3 g of p-toluenesulfonic acid chloride in 300 mL of chloroform with a water separator were heated for 20 h. The chloroform layer was subjected to acid washing, alkali washing, and water washing, then dried and concentrated. It was then recrystallized from 70% alcohol to obtain 24.1 g of the desired product with a melting point of 141-142°C.

Elemental analysis

	Theoretical value	Analytical value
C (%)	81.47	81.49
H (%)	7.22	6.93
N (%)	5.28	5.24

Application Example 2

14.8 g of cinnamic acid, 13.5 g of α-p-dimethylbenzylamine, and 21.6 g of dicyclohexyl carbodiimide were dissolved in 300 mL of chloroform. It was allowed to stand as is at room temperature for one night. A small amount of acetic acid was added to remove excess dicyclohexyl carbodiimide. The precipitate was filtered off. The filtrate was treated in the same manner as in Application Example 1 to obtain 22.6 g of the desired product with a melting point of 142-143°C.

Elemental analysis

	Theoretical value	Analytical value
C (%)	81.47	81.51
H (%)	7.22	7.14
N (%)	5.28	5.26

Application Example 3

The reaction was continued for 32 h by the addition of 14.8 g of cinnamic acid and15 g of α-p-dimethylbenzylamine, while water forming as a by-product at 180°C was being driven off. After completion of the reaction, it was dissolved in chloroform and treated in the same manner as in Application Example 1 to obtain 23.5 g of the desired product with a melting point of 141-142°C.

Elemental analysis

	Theoretical value	Analytical value
C (%)	81.47	81.45
H (%)	7.22	7.31
N (%)	5.28	5.22

Application Example 4

To 16.2 g of cinnamic acid methyl ester and 13.5 g of α-p-dimethylbenzylamine, 0.3 g of sodium methylate was added. It was heated and stirred at 140°C for 4 h.

After the completion of the reaction, it was treated in the same manner as in Application Example 1 to obtain 24.0 g of the desired product with a melting point of 140-141°C.

Elemental analysis

	Theoretical value	Analytical value
C (%)	81. 47	81.30
H (%)	7.22	7.21
N (%)	5.28	5.21

Application Example 5

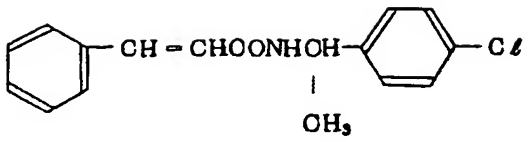
16.1 g of cinnamic acid chloride were added dropwise into 13.5 g of α-p-dimethyl benzyl amine, 9 g of trimethylamine, and 200 cc of chloroform at 0°C to 5°C. After completion of the reaction, it was allowed to stand as such at room temperature for one night. It was treated in the same manner as in Application Example 1 to obtain 25.9 g of the desired product with a melting point of 142-143°C.

Elemental analysis

	Theoretical value	Analytical value
C (%)	81.47	81.40
H (%)	7.22	7.02

N (%)	5.28	5.26

From the methods in Application Example 1 through Application Example 5, the following compounds were obtained.

(1) 

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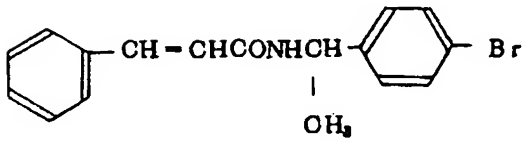
(2) 

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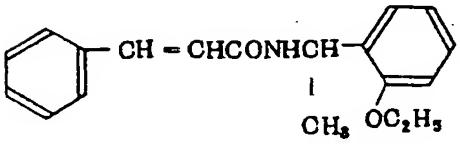
(3) 

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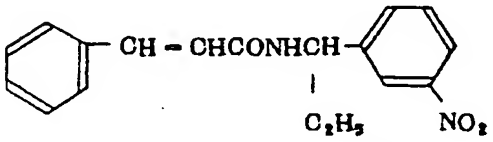
(4) 

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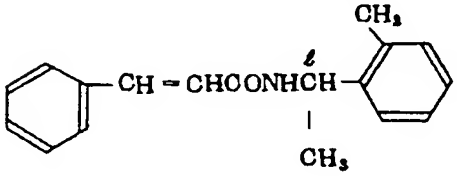
(5) 

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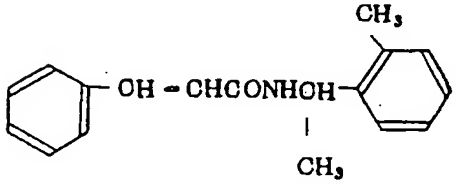
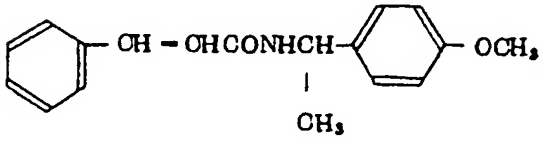
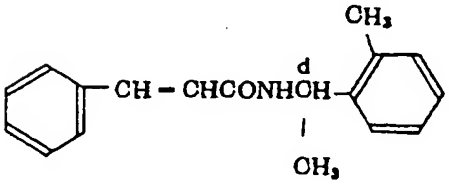
(6) 

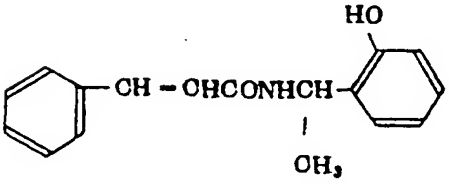
融点１４０～１４２℃

(7) 

融点１０９～１１２℃

(8) 

融点１４０～１４２℃

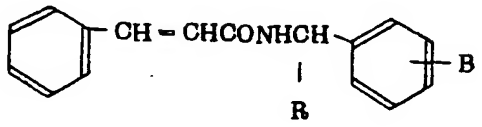
(9) 

融点１６２～１６３℃

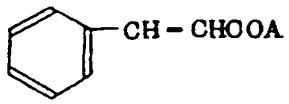
Key: 1 Melting point _____

Claim

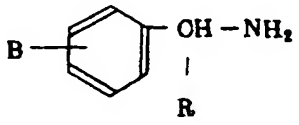
1. A method for the manufacture of a novel cinnamic acid amide represented by the following general formula:



(in this formula, R represents a lower alkyl group, and B represents an oxy group, a lower alkoxyl group, a lower alkyl group, a nitro group or a halogen atom) characterized by the fact that cinnamic acid or its reactive derivatives represented by the following general formula:



(in this formula, A represents an oxy group, a halogen atom, or a lower alkoxyl group) is reacted with a racemic d or l substituted α-lower alkylbenzylamine represented by the following general formula:



(in this formula, R and B are the same as described above).

(52)日本分類
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30 B 4

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(11)特許出願公告
昭45－14291

(10)特許公報

(44)公告 昭和45年(1970)5月21日
発明の数 1
(全4頁)

1

(54)新規桂皮酸アミド体の製法

(21)特願 昭42－44594
(22)出願 昭42(1967)7月10日
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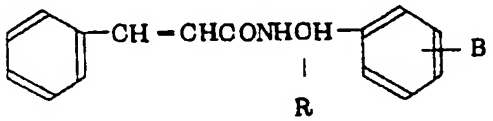
発明の詳細な説明

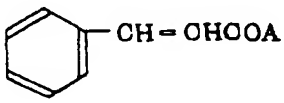
本発明は一般式(I)



(I)

(式中、Rは低級アルキル基を、Bはオキシ基、低級アルコキシル基、低級アルキル基、ニトロ基もしくはハロゲン原子を表わす)
にて示される新規桂皮酸アミド体の製法に関するものである。

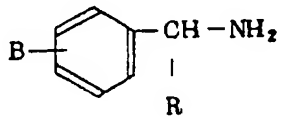
さらに詳しく説明するならば、本発明は一般式(II)



(II)

(式中、Aはオキシ基、ハロゲン原子もしくは低級アルコキシル基を表わす。)
にて示される桂皮酸またはその反応性誘導体と一般式(III)

2



(III)

(式中、RおよびBは前述のとおりである。)
にて示される置換α－低級アルキルベンジルアミンとを反応させ、上記一般式(I)で示される新規桂皮酸アミド体を得る方法に関するものである。

本発明方法により得られる化合物は文献未記載の新規化合物であり、本物質群は著効な降圧、消炎鎮痛作用を有するものである。

本発明の目的は、かかる有用な化合物を工業的に有利に製造することにある。

本発明方法で使用する原料物質として、たとえば次の置換基を有するものがある。すなわち、

B:ヒドロキシ、メチル、エチル、n－プロピル、i－プロピル、n－ブチル、i－ブチル、t－ブチル、メトキシ、エトキシ、n－プロポキシ、i－プロポキシ、n－ブトキシ、i－ブトキシ、t－ブトキシ、フッ素、クロル、ブロム、ヨード、ニトロ

R:メチル、エチル、n－プロピル、i－プロピル、n－ブチル、i－ブチル、t－ブチル

A:ヒドロキシ、クロル、ブロム、ヨード、メトキシ、エトキシ、n－プロポキシ、i－プロポキシ、n－ブトキシ、i－ブトキシ、t－ブトキシなどが挙げられる。

次に反応の様態を個々に説明すれば、桂皮酸を使用する場合は、大約当モルの桂皮酸とアミノと脱水助剤としてはジメチル、エチル、プロピル、ブチル等のアルキルカルボジイミド、ジフエニールカルボジイミド、ジベンジルカルボジイミド、ジシクロペンチル、ヘキシル、ヘプチル等のアルキルカルボジイミド等を適当な溶剤中たとえばベンゼン、トルエン、キシレン等の芳香族系炭化水素、石油エーテル、石油ベンジン、リグロイン、ガソリン、ペンタン、ヘキサン、ヘプタン、シクロペンタン、シクロヘキサン、シクロヘプタン等の脂

3

肪族炭化水素、エチルエーテル、プロピルエーテル、テトラヒドロフラン、ジオキサン等エーテル類、酢酸メチル、酢酸エチル、酢酸プロピル、酢酸ブチル等のエステル類、アセトン、メチルエチルケトン、メチルーブチルケトン等のケトン類、ジクロルメタン、ジクロルエタン、クロロホルム、四塩化炭素等のハロアルカン類、メチルアルコール、エチルアルコール等のアルコール類中で反応させれば目的物を得ることができる。また桂皮酸とアミンとイオン交換樹脂たとえばＩＲＡ－400その他の陰イオン、陽イオン交換樹脂とベンゾール、トルエン、キシレン等と水分離器を必要に応じて使用して加熱反応させてもよいし、また桂皮酸とアミンとたとえばｐ－トルエンスルホン酸またはｐ－トルエンスルホン酸クロライド等とベンゼン、トルエン、キシレン、クロロホルム、四塩化炭素、ピリジン、ルチジン等中において必要に応じて水分離器を用いて加熱反応させても目的物を得ることができる。さらにまた桂皮酸とアミンとの混合物は脱水助剤の存在下、または非存在下に単に加熱または蒸留しても目的物を得ることができる。

桂皮酸の低級アルキルエステルを使用する場合は、アミンと無溶媒または必要に応じて、ベンゾール、トルエン、キシレン等の芳香族系炭化水素、石油エーテル、石油ベンジン、ガソリン、リグロイン、ペンタン、ヘキサン、ヘプタン、シクロペンタン、シクロヘキサン、シクロヘプタン等の脂肪族系炭化水素、メチルアルコール、エチルアルコール、プロピルアルコール、ブチルアルコール等のアルコール類、エーテル、テトラヒドロフラン、ジオキサン等の溶媒中で無触媒でまたは必要に応じてリチウム、ナトリウム、カリウム等のメチラート、エチラート、プロピラート、ブチラート等のアルカリ触媒、ピリジン、ルチジン、ピコリン、トリメチルアミン、トリエチルアミン、ジメチルアニリン、ジメチルアニリン等の第三有機アミンを触媒として５０℃から４００℃位の加熱範囲で常圧下またはオートクレーブ中で３０分から約１カ月位の反応時間で目的を達成することができる。反応中に生じたアルコール類を系外に導入することが望ましいが、必ずしも必要ではない。

桂皮酸ハライドとの反応は塩化チオニール、ホスゲン、その他の方法で製造した酸クロライド、酸ブロマイド等と適当な溶媒たとえばベンゼン、

4

トルエン、キシレン等の芳香族系炭化水素、石油エーテル、石油ベンジン、リグロイン、ガソリン、ペンタン、ヘキサン、ヘプタン、シクロペンタン、シクロヘキサン、シクロヘプタン等の脂肪族系炭化水素、クロロホルム、四塩化炭素等のハロアルカン中、アセトン、メチルエチルケトン、メチルブチルケトン等のケトン類、酢酸メチル、酢酸エチル、酢酸プロピル、酢酸ブチル等のエステル中において、苛性リチウム、苛性ナトリウム、苛性カリ、水酸化カルシウム、炭酸リチウム、炭酸ナトリウム、炭酸カリウム、炭酸カルシウム、重炭酸リチウム、重炭酸ナトリウム、重炭酸カリウム等のアルカリ金属、アルカリ土類金属化合物塩またはピリジン、ピコリン、ルチジン、トリメチルアミン、トリエチルアミン、ジメチルアニリン、ジエチルアニリンその他の第三アミン類等を助剤として用いて反応すれば極めて容易に目的物を得ることができる。

以下実施例につき説明を行うがこれらは限定的な意味を持つものではない。

実施例　1

桂皮酸１４.８ｇ、α・ｐ－ジメチルベンジルアミン１３.５ｇおよびｐ－トルエンスルホン酸クロライド0.3ｇをクロロホルム３００㎖中水分離器を付して２０時間加熱する。クロロホルム層は酸洗、アルカリ洗、水洗、乾燥濃縮後、７０％アルコールより再結晶を行い融点１４１－１４２℃の目的物２４.１ｇを得た。

元素分析

	理論値	分析値
C (%)	81.47	81.49
H (%)	7.22	6.93
N (%)	5.28	5.24

実施例　2

１４.８ｇの桂皮酸および１３.５ｇのα・ｐ－ジメチルベンジルアミンおよび２１.６ｇのジシクロヘキシルカルボジイミドをクロロホルム３００㎖中に溶解しそのまま一夜室温に放置した。少量の酢酸を加えて過剰のジシクロヘキシルカルボジイミドを除いて沈殿を濾去し、濾液を実施例１と同様に処理して融点１４２～１４３℃の目的物２２.６ｇを得た。

元素分析

	理論値	分析値
C (%)	81.47	81.51

5

H (%)	7.22	7.14
N (%)	5.28	5.26

実施例 3

14.8 g の桂皮酸および15 g のα・p－ジメチルベンジルアミンを加え180℃に副生する水を駆逐しながら反応を32時間続けた。反応終了後、クロロホルムに溶解し実施例1と同様処理して融点141～142℃の目的物23.5 g を得た。

元素分析

	理論値	分析値
C (%)	81.47	81.45
H (%)	7.22	7.31
N (%)	5.28	5.22

実施例 4

16.2 g の桂皮酸メチルエステルおよび13.5 g のα・p－ジメチルベンジルアミンに0.3 g のナトリウムメチラートを加え140℃に4時間加熱撹拌した。

反応終了後実施例1と同様に処理して、融点140～141℃の目的物24.0 g を得た。

6

※ 元素分析

	理論値	分析値
C (%)	81.47	81.30
H (%)	7.22	7.21
N (%)	5.28	5.21

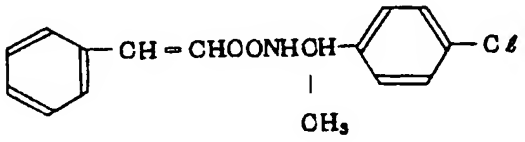
実施例 5

桂皮酸クロライド16.1 g をα・p－ジメチルベンジルアミン13.5 g、トリメチルアミン9 g 及びクロロホルム200 cc中0℃～5℃で撹拌下に滴下した。反応終了後、一夜室温に放置し実施例1と同様に処理して融点142～143℃の目的物25.9 g を得た。

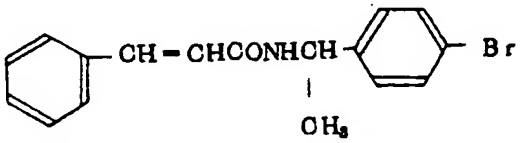
元素分析

	理論値	分析値
C (%)	81.47	81.40
H (%)	7.22	7.02
N (%)	5.28	5.26

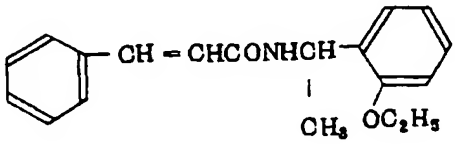
実施例1～実施例5の方法により下記の化合物を得た。

(1) 

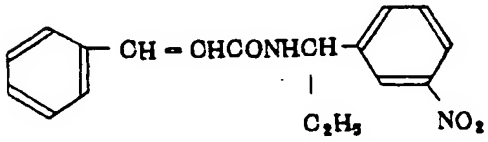
融点122～123℃

(2) 

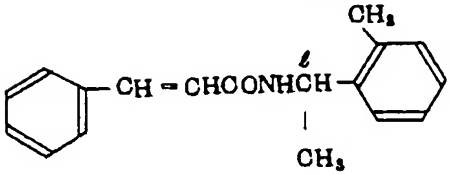
融点131～133℃

(3) 

融点113～114℃

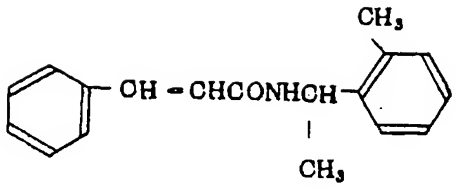
(4) 

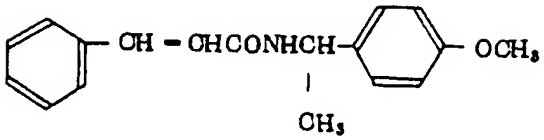
融点129～132℃

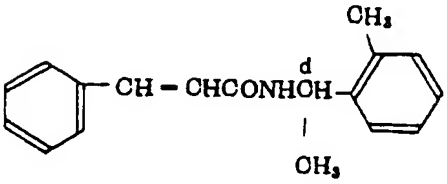
(5) 

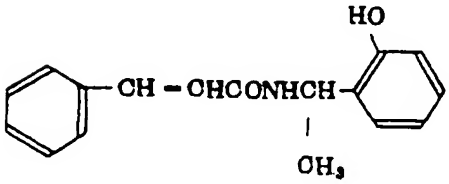
融点140～141℃

7　　8

(6)  　融点140～142℃

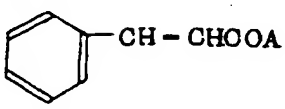
(7)  　融点109～112℃

(8)  　融点140～142℃

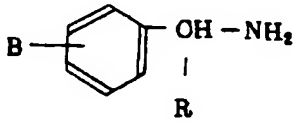
(9)  　融点162～163℃

特許請求の範囲

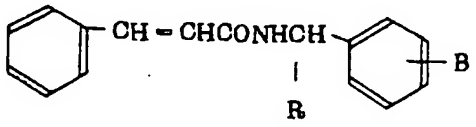
1　次の一般式



（式中、Aはオキシ基、ハロゲン原子、低級アルコキシル基をあらわす。）にて示される桂皮酸またはその反応性誘導体と次の一般式



（式中、Rは低級アルキル基を、Bはオキシ基、低級アルコキシル基、低級アルキル基、ニトロ基もしくはハロゲン原子をあらわす。）にて示されるラセミ型、d型もしくはl型置換α－低級アルキルベンジルアミンとを反応させることを特徴とする次の一般式



（式中、RおよびBは前述のとおりである。）にて示される新規桂皮酸アミド体の製法。